REMARKS

In this 1st Official Action, the Examiners have objected to the Specification and claims for failing to adhere to the requirements of the sequence rules. In addition, the Examiners have rejected independent claim 11 under 35 USC 112, first paragraph, as failing to comply with the written description requirement. Finally, the Examiners have rejected independent claim 11 under 35 USC 103(a), as being unpatentable over the Ross '233 patent reference.

In response, applicants have amended claims 11 and 15-16 respectively. Accordingly, by the present amendments to the claims as well as by the discussion presented hereinafter, applicants believe they have overcome and obviated each basis for objection and rejection stated by the Examiners in the instant 1st Official Action.

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Applicants and their undersigned attorney wish to state their intentions clearly to the Examiner of record. It is our express desire and purpose to advance the prosecution of their application on the merits, and not to delay or hinder its progress.

To achieve this goal, applicants have therefore amended claims 11 and 15-16 respectively of the application; and, via such amendment, markedly altered the size definition of the members constituting the PR-39 derived

oligopeptide family. Concomitant with these claim amendments, applicants will also directly address and substantively review herein each basis for objection and rejection stated by the Examiners in the instant Official Action, as well as provide an accurate and proper basis for their resolution.

I. The Objection To The Claims

The Examiners have objected to the Specification and the previously presented claims as failing to adhere to the requirements of the sequence rules as set forth by 37 CFR 1.821(d).

In response, applicants have added individual SEQ ID NO. identifications to each of dependent claims 15 and 16 respectively. As currently amended, the wording of claim 15 now ends with "(SEQ ID NO:4)"; and the language of claim 16 now ends with "(SEQ ID NO:5)". These individual sequence identifications conform exactly to those sequence numbers previously entered into the Specification text at page 26, lines 27 and 32.

Applicants also direct the Examiners' attention to the fact that all necessary sequence identification numbers were added previously into the original Specification text via the Amendments submitted March 28, 2002, which were a part of the formal Reply to the Notice Of Non-Compliant Amendment (mailed March 21, 2002) for the above-identified application. A

complete set of marked-up and clean copy versions of multiple substitute pages were submitted at that time (March 28th, 2002) for formal entry into and merger within the original Specification text. These multiple substitute pages added individual SEQ ID NOS. to the paragraphs of the Specification appearing at: page 24, line 13; page 26, lines 14, 22, 27, and 32; page 28, Table 4; and page 46, line 9. Thus, all the requirements of appending SEQ ID NOS. to the Specification were met and fulfilled in complete accordance with 37 CFR 1.821 on March 28th, 2002.

Based on all the foregoing, applicants respectfully request that the Examiners reconsider their stated position and withdraw this ground of objection against the presently pending claims

II. The Written Description Rejection Under 35 USC 112, 1st Paragraph

The Examiners have twice rejected previously pending claim 11 as failing to comply with the written description requirement. The Examiners, however, have presented two very different reasons for rejection. These two reasons are given in the following words:

> Reason 1: "The claims(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" [page 3, bottom, of the Official Action]....

Reason 2: "There are two species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.,* SEQ ID NO:4 AND SEQ ID NO:5. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. There is substantial variability among the species." [page 5, top, of the Official Acton]

In reply, applicants respectfully submit that both of the Examiners' stated views and positions are misplaced and erroneous in fact and law. Taking the Examiners' own words at their face value, it appears that the Examiners are struggling to identify properly and to explain clearly what is the true underlying factual reason for the new rejection. Moreover, the Examiners also appear to be conceptually wrestling with two very different legal doctrines in order to find some ostensible support in law for their rejection.

In support of their position, applicants and their undersigned attorney will now demonstrate and evidence the nature of the different legal and factual errors undercutting each of the two different reasons for rejection stated by the Examiners.

A. A fairly uniform legal standard presently exists for determining if the written description requirement of 35 USC 112, 1st paragraph has been complied with and been sufficiently satisfied by the disclosure (the entire

Specification text and Drawing, if any) in an application.

1. The caselaw decisions to date state that the proper legal test for sufficiency of descriptive support is whether or not the disclosure in the pending application conveys to a person of ordinary skill in that art that the inventor had "possession" of the innovative subject matter as a whole , as then defined by the claims. Thus, to be legally sufficient, the written description in its entirety must clearly contain and communicate enough knowledge, information, and detail to allow a person of ordinary skill in the technical field to recognize that the applicant invented that which is claimed [In re Gosteli, 10 USPQ2d 1614 (Fed. Cir. 1989); In re Kaslow, 217 USPQ 1089 (Fed. Cir. 1983)].

2. For this determination, fact specificity is central and essential to deciding the issue. Thus, when considering the legal sufficiency of the written description, the primary inquiry for the Examiner in each instance is to evaluate the quality and quantity of factual detail actually provided by the disclosure. These parameters, in turn, will vary with and depend upon the nature and substance of the invention; and also will indicate the amount and kind of information and detail which is necessary to be present within the disclosure for the invention to be imparted to and recognized by a person of ordinary skill in the art [In re Wertheim, 169 USPQ 795 (CCPA 1971); Vas-

Cath Inc. Vs. Makurkar, 19 USPQ2d 1111 (Fed. Cir. 1991) and the reference citations listed therein at page 116].

3. All the caselaw decisions to date routinely point out and emphasize that the written descriptive requirement of Section 112, 1st paragraph is an issue which must be decided in each instance on its own facts, with proper regard for the subject matter as a whole constituting the specific invention, and with due consideration of the state of conventional knowledge then existing within that art or technical field.

4. Overall therefore, full compliance with and satisfaction of this legal requirement asks merely that the written description of the Specification, when reviewed in its entirety, present and provide the reader with useful information and sufficient detail of what the applicant holds and considers as his own invention - in such degree that the invention as disclosed and claimed can be understood in full and clearly distinguished from that knowledge which is conventionally known or is in common use [In re Smith & Hubin, 178 USPQ 620 (CCPA 1973); In re Wright, 9 USPQ2d 1649 (Fed. Cir. 1989); Ralston Purina Co. Vs. Far-Mar-co Inc., 227 USPQ 177 (Fed. Cir 1985); Vas-Cath Inc. Vs. Makurkar, 19 USPQ2d 1111 (Fed. Cir. 1991)].

B. Applicants also respectfully maintain that the written descriptive requirement of Section 112, 1st paragraph has multiple legal purposes and makes a second legal demand of the applicant. Thus, in addition to the legal duty identified by Section A above, there is a second and different legal obligation to be fulfilled. It is therefore necessary for the Examiners to understand correctly what this second different legal obligation is; as well as to appreciate fully what are the proper legal standards concerning the written description requirement and its relationship to the scope of the claim language defining the invention. For this purpose, a summary review of the "adequacy of written description" legal principles is presented below.

1. One specific purpose of the written description requirement is to prevent an applicant from later asserting that the applicant invented that which he did not. An applicant for a patent is therefore required to recount his invention in such detail that applicant's future claims can be determined to be encompassed within applicant's originally described creation [Amgen Inc. vs. Hoechst Marion Roussel Inc., 65 USPQ2d 1385 at 1397 (Fed. Cir. 2003); Vas-Cath Inc. vs. Mahurkar, 19 USPQ2d 1111 at 1115 (Fed. Cir. 1991)].

2. Satisfaction of the written description requirement for this purpose is measured by the understanding of a person having ordinary skill in the art. The description disclosed by the Specification text and the Drawing (if

any) must clearly be adequate to allow persons of ordinary skill in the art to recognize that the inventor actually invented what is claimed [Lockwood vs. American Airlines Inc., 41 USPQ2d 1961 at 1966 (Fed. Cir. 1997)].

3. The proper test for determining whether the later claimed subject matter is supported by an earlier presented written description is: Whether the disclosure of the application reasonably conveys to a person skilled in the art that the inventor has possession of the additionally claimed subject matter at the time of the application's filing [Union Oil of California vs. Atlantic Richfield Co., 54 USPQ2d 1227 at 1232 (Fed. Cir. 2000); Eiselstein vs. Frank, 34 USPQ2d 1467 at 1470 (Fed. Cir. 1995); Ralston Purina Co. vs. Far-Mar Co. Inc., 227 USPQ 177 at 170 (Fed. Cir. 1985); In re Kaslow, 217 USPQ 1089 at 1096 (Fed. Cir 1983)].

Note however, that this test is separate and distinct from the "possession of the invention" inquiry of the written description requirement; and the adequacy of description requirement is not subsumed by the "possession" inquiry [New Railhead Mfg. LLC vs. Vermeer Mfg. Co., 63 USPQ2d 1843 at 1847 (Fed. Cir. 2002)].

Thus, a showing of "possession of the invention" is ancillary to the statutory mandate that the Specification shall contain a written description of the invention; and that this requirement is not met, despite a showing of "possession", if the Specification does not adequately describe the claimed

invention [Enzo Biochem. Inc. Vs. Gen-Probe Inc., 63 USPQ2d 1609 at 1617 (Fed. Cir. 2002)].

4. Accordingly, in order to satisfy the "adequacy of written description" as a separate and distinct legal requirement, the Specification need only provide information in sufficient quantity and quality such that persons having ordinary skill in the art can recognize that the applicant invented the later claimed subject matter [Union Oil of California vs. Atlantic Richfield Co., 54 USPQ2d 1227 at 1232 (Fed. Cir. 2000); In re Gosteli, 10 USPQ2d 1614 at 1618 (Fed. Cir. 1989)]. The adequacy of the written description is measured from the totality of the disclosure in the application; and the description of the invention as a whole must show that the applicant invented each feature that is recited as a claim limitation; and [New Railhead Mfg. LLC vs. Vermeer Mfg. Co., 63 USPQ2d 1843 at 1847 (Fed. Cir. 2002)].

In addition, the ordinarily skilled person in the art must reasonably be able to discern the limitation at issue in the claims; and a broadly drafted claim, if presented, must be fully supported by the Specification text and the Drawing, if any [Crown Operations Int'l. Ltd. vs. Solutia Inc., 62 USPQ2d 1917 at 1922 (Fed. Cir. 2002); Waldemar Link GmbH & Co. vs. Osteonics Corp., 31 USPQ2d 1855 at 1857 (Fed. Cir. 1994); Amgen Inc. vs. Hoechst Marion Roussel Inc., 65 USPQ2d 1385 at 1397 (Fed. Cir. 2003)].

5. Furthermore, in order to comply with the adequacy of written description requirement, the Specification need not describe the claimed subject matter in exactly the same terms as used in the claims. Rather, the written text must simply demonstrate to persons ordinarily skilled in the art that, as of the filing date, the applicant had invented that which is now claimed [All Dental Prodx LLC vs. Advantage Dental Products Inc., 64 USPQ2d 1945 at 1948 (Fed. Cir. 2002); In re Wertheim, 191 USPQ 90 at 98 (CCPA 1976)].

The failure of a Specification text to mention a limitation that later appears in the claims is not fatal - if one skilled in the art, after reading the Specification text, would recognize that the newly presented claim language reflects what the Specification shows has been invented [Eiselstein vs. Frank, 34 USPQ2d 1467 at 1470 (Fed. Cir. 1995)].

Thus, while *in haec verba* identity between the word text of the Specification and the language of the claims is not required, substantive sameness between the subject matter defined by the claims and that which is described by the Specification is necessary; and what is claimed by the patent application must be substantively equal to what is disclosed by the Specification [New Railhead Mfg. LLC vs. Vermeer Mfg. Co., 63 USPQ2d 1843 at 1847 (Fed. Cir. 2002)].

C. In view of all the foregoing, applicants have therefore substantively amended the recited scope of previously pending independent claim 11. As now defined, amended independent claim 11 recites a carefully circumscribed and size-limited membership of PR-39 analog compositions, each of which is not substantially greater than 11 amino acid residues in length.

Amended independent claim 11 thus encompasses and comprises a size-restricted family of PR-39 analog compositions which is severely limited in number; and whose members are pharmacologically active; and whose membership is operative to cause a selective inhibition of proteasome-mediated degradation in-situ after being introduced intracellularly to a viable cell. Moreover, the commonly-shared characteristics and properties of the size-restricted family members are overtly stated and individually set forth as requisite elements and specific limitations by the language of currently amended independent claim 11.

In addition, two exemplary embodiments of this size-restricted family of oligopeptides are identified and defined by previously pending dependent claims 15 and 16 respectively. Amended dependent claim 15 recites a precisely stated sequence of 11 amino acid residues; and amended dependent claim 16 delineates a precisely recited sequence of 8 amino acid residues. It is noted that the current amendments to each of these dependent claims have merely added the appropriate sequence identification

number for each. Accordingly, the size-restricted family membership defined by currently amended independent claim 11 properly encompasses the exemplary 11 and 8 residue length embodiments; and illustrates the intended scope and range of coverage for the claims now pending in the instant application.

D. Equally important, the written description provides more than abundant factual support for each of the elements and limitations recited by claims 11 and 15-16 respectively. Full information and detailed knowledge of the invention defined by currently amended claims 11 and 15-16 is to be found at pages 24-27 of the Specification; and empirical operative support for these claims is demonstrated by Experiment 6, described at page 46 of the Specification text.

Overall therefore, the Specification text provides full compliance and satisfaction of both written description legal requirements. When reviewed in its entirety, the Specification provides the reader with useful information and sufficient detail of what the applicant holds and considers as his own invention - in such degree that the invention as disclosed and claimed can be understood in full and clearly distinguished from that knowledge which is conventionally known or is in common use.

Upon this probative showing and evidence, it is therefore abundantly clear that the written description of the Specification is more than sufficient

to support the definitions of applicants' invention as currently recited by amended claims 11 and 15-16 respectively. Applicants thus affirm that they had "possession" of the presently claimed invention at the time the instant application was filed.

In addition, the written description as a whole disclosed by the Specification text is adequate in descriptive value, is coextensive in scope, and is equal in coverage with the amended language of the presently pending claims. Applicants thus affirm that the subject matter which is within the scope of the presently pending claims is substantively equal to and is properly commensurate with that which is disclosed by the Specification.

For these reasons, applicants respectfully submit that each and every claim now pending satisfies the written description requirements of the 1st paragraph of 35 USC 112. Accordingly, applicants respectfully request that the Examiners reconsider their stated position and withdraw this ground of rejection against the presently pending claims.

III. The Rejection Under 35 USC 103(a)

The Examiners have rejected independent claim 11 under 35 USC 103(a) as being unpatentable over the Ross *et al.* '233 patent [U.S. Patent No. 6,133,233]. However, applicants respectfully submit and maintain that

the Examiners have yet to recognize or appreciate the subject matter as a whole which is currently defined by amended claim 11. Instead, applicants respectfully submit that the Examiners have conducted an unbalanced review and presented applicants with a view and position which is factually inaccurate and legally improper.

Applicants will therefore demonstrate and evidence the nature and substance of these prejudicial errors.

A. As a matter of long established caselaw decisions, the proper legal basis and requisite test for determining obviousness under Section 103(a) must include and consider, *inter alia,* two particular factors: (1) Whether the prior art of record would have suggested to those of ordinary skill in the art that they should make and use the claim composition; and (2) whether the prior art of record would also have revealed that in so making and using, those of ordinary skill would have a reasonable expectation of success [In re Dow Chemical co., 5 USPQ2d 1529 (Fed. Cir. 1988)]. Note that both the suggestion and the reasonable expectation of success must be found within the prior art reference(s) itself and not in applicants' disclosure [In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991)].

Equally important, the same inquiry must be carried out in the context of a purported "obvious modification" of the prior art information. The mere fact that the prior art information might be modified in the manner

suggested by the Examiners does not make that modification obvious unless the prior art itself suggested the desirability of that modification [In re Fritch, 23 USPQ2d 1780 (Fed. Cir. 1992) and the cases internally cited therein].

Applicants respectfully submit and maintain that the Examiners' views and conclusions as expressed in the instant Official Action do not meet or satisfy the legal burden and standard required to reach a conclusion that applicants' presently claimed invention is obvious.

B. Applicants also maintain and affirm that the factual content of the Ross *et al.* '233 patent does not meaningfully pertain to the invention defined by the currently amended clams. Applicants' position is clearly evidenced and demonstrated by an objective reading of the '233 patent disclosure, and by the very limited information revealed in the '233 patent which is material to applicants' claimed invention. Applicants therefore direct the Examiners' attention to the following facts:

1. The Ross *et al.* '233 patent teaches the use of markedly different compositions of matter which are suitable as a class of compounds for effecting a single purpose - reducing reperfusion injury resulting from temporary occlusion of a blood vessel in a living mammal [Column 1, lines 17-20; Column 2, lines 22-26]. The sole objective and explicitly stated goal of the Ross *et al.* invention is to inhibit the indices of reperfusion injury - *i.e.,*

inhibiting the production of reactive oxygen species, and inhibiting neutrophil adherence to endothelium, as well as inhibiting extravasation of neutrophils, all of which result from reperfusion in-vivo [Column 1, lines 28-31 and 42-63].

2. The methodology described and defined by the Ross *et al.* '233 patent explicitly sets forth two carefully recited manipulative steps as the essence of the invention: (i) administering into the mammal's bloodstream a reperfusion injury-reducing amount of a peptide having up to about 50 amino acid residues, at least 65% of which are proline and arginine residues' and (ii) allowing the peptide administered to the blood to come into effective contact with the temporarily occluded blood vessel in order to minimize the degree of reperfusion injury [Column 2, lines 22-32; Claim 1].

3. The Ross et al. invention is thus dependent upon an a peptide's capability to counteract the effects of oxygen-derived free radicals - which are typically released during reperfusion injury after the temporary occlusion of a blood vessel has been removed. The released oxygen-derived free radicals are said to be the primary mechanism of oxidation damage to cell structures; and the effect is caused by reactive oxygen species (such as a superoxide ion) which are central to these events during the reperfusion of temporarily occluded blood vessels [Column 1, lines 47-54 and 64-67]. For

this reason also, the disclosed experiments and empirical results analytically measure the generation of reactive oxygen intermediate species [Column 5, lines 52-60].

4. The Ross *et al.* '233 patent discloses that a number of markedly different peptide compositions constitute the class of peptides which is active and suitable for administration to a living mammal in order to reduce reperfusion injury. The exemplary peptide compositions include Bac 5, Bac 7, C7, and PAF [see Fig. 5]; as well as the native PR-39 peptide and its longer length peptide analogues known conventionally as "synducins" - which are a distinct family of oligopeptides previously recognized in the art as being able to induce the expression of proteoglycans in mesenchymal cells [see PCT Publication WO 96/09322 expressly included by reference within the '233 patent]. Of all the disclosed peptide compositions, the PR-39 peptide is by far the most preferred for use to reduce reperfusion injury [Column 2, lines 44-45; Column 4, line 66 through Column 6, line 67].

5. The Ross *et al.* '233 patent also teaches what are generally the structural requirements for the peptide compositions which are deemed to be suitable for use to effect a reduction of reperfusion injury in-vivo. These general structure requirements for the peptide include:

(a) The peptide desirably comprises up to 50 amino acid residues, where at least 60% (and preferably 65-80%) of the residues are proline and arginine [Column 2, lines 32-55].

(b) The peptide must have at least one amino acid sequence of PXXP, and preferably has at least four PXXP sequences, where P is proline and X is any amino acid residue; and should also have one or more basic amino acids within six residues (and preferably within three residues) from both the starting and terminal proline residues of the PXXP sequence [Column 2, lines 56-76; Column 3, lines 1-11].

6. The Ross *et al.* '233 patent also attempts to describe more broadly what are the range of peptides which might be suitable for use in their method to effect a reduction of reperfusion injury in-vivo. Thus, the text of the '233 patent openly states that: "...The preferred peptides are selected from the group consisting of the peptides of SEQ ID NOS:1-11..." [Column 2, lines 41-43]. Among these identified sequences is SEQ ID NO:4, which recites a 14 amino acid residue analog of PR-39 peptide [Column 9, bottom].

Curiously however, this is almost all the information disclosed by the '233 patent text; specifically, the only other description detail given within the '233 patent about SEQ ID NO:4 is merely the mathematical percentages of arginine and proline in this sequence, which is stated as "NO:4(12/14, 86%" [Column 2, line 48].

This is the totality of relevant information disclosed within the entirety of the '233 patent about this 14 amino acid residue sequence.

C. The factual summary given above presents the sum and substance of the knowledge that is taught or suggested by the disclosure of the Ross *et al.*'233 patent to a person of ordinary skill in the art. The Examiners thus rely completely and unequivocally upon two bare facts in the cited and applied patent reference: (i) SEQ ID NO:4 recites a 14 amino acid residue analog of PR-39 peptide ; and (ii) the mathematical percentages of arginine and proline residues existing within the peptide recited by SEQ ID NO:4 sequence is 86%.

Applicants respectfully submit and maintain, however, that these disclosed facts do not bear upon and are not relevant to the invention defined by currently amended independent claim 11. In particular, nothing disclosed in the Ross *et al.* '233 patent implies or forecasts the restricted peptide size requirements, nor the requisite pharmacological activity, nor the functions and capabilities of a family of PR-39 derived oligopeptides able to cause a selective inhibition of proteasome-mediated degradation. Equally important, no mathematical percentages of proline and arginine can serve as a predictor of which peptides can cause a selective inhibition of proteasome-mediated degradation after being introduced intracellularly to a viable cell.

Applicants therefore submit that the requisite attributes and

characteristics of applicants' invention as currently claimed cannot be inferred and cannot be foreseen by any ordinarily skilled person from the limited information provided by the disclosure of the Ross *et al.* 233 patent. Accordingly, the underlying rationale stated by the Examiners is thus not based upon demonstrable fact, but represents only mere whim and caprice. There is no underlying factual basis whatsoever to support the Examiners' stated conclusions.

D. In view of all the foregoing, and in particular to prevent a recurrence of Examiners' whimsy, applicants have therefore substantively amended the recited scope of previously pending independent claim 11. As now defined, amended independent claim 11 recites a carefully circumscribed and size-limited membership of PR-39 analog compositions which are not substantially greater than 11 amino acid residues in length.

As currently worded, amended independent claim 11 thus encompasses and comprises a size-restricted family of PR-39 analog compositions whose numbers are severely limited; whose members are pharmacologically active; and whose membership as a family is operative to cause a selective inhibition of protease-mediated degradation in-situ after being introduced intracellularly to a viable cell. Moreover, the commonly-shared characteristics and properties of the size-restricted family members are overtly stated and individually set forth as requisite elements and

specific limitations by the language of currently amended independent claim 11.

The patentable merit of the invention defined by currently amended claim 11 is plain and unequivocal. In comparison with the cited and applied Ross *et al.* '233 patent, applicants' claimed invention stands apart and alone in its unique worth and unforeseen value.

For these reasons, applicants respectfully submit that each and every claim now pending satisfies the non-obvious requirement of 35 USC 103(a). Accordingly, applicants respectfully request that the Examiners reconsider their stated conclusion and withdraw this ground of rejection against the presently pending claims.

IV. Summary Of Applicants' Response

In sum, applicants have addressed each basis of objection and rejection stated in the 1st Official Action forthrightly and objectively. In applicants' view, each relevant question or issue has been acted upon and resolved completely. For these reasons, applicants respectfully submit and affirm that each of claims 11 and 15-16 now pending are therefore allowable.

In view of the above discussion and detailed review, applicants believe that this application is now in condition for allowance and reconsideration is respectfully requested. The Examiners are invited to call applicants'

undersigned attorney should they feel that such a telephone call would further the prosecution of the present application.

Respectfully submitted,

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Date: Dec. 14, 2005

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